a sulfated polysaccharide which inhibits angiogenesis.

Please add new claim 18.

18. The method of claim 10 wherein the disorder is malignant melanoma.

Remarks

Information Disclosure Statement

Please note that an Information Disclosure Statement was filed with this application but that the PTO 1449 forms have not been intialled and returned to the undersigned.

Double Patenting Rejection

Claims 4-6, 10-12, and 17 were provisionally rejected over claims 4, 5, 7, 9 and 17 of co-pending application No. 09/345,712. Although claims 4, 5, 7, 9 and 17 of the co-pending application have been cancelled, a Terminal Disclaimer is enclosed to facilitate prosecution.

Rejection under 35 U.S.C. 112

Claims 10-12 were rejected under 35 U.S.C. 112 as indefinite. This rejection is respectfully traversed.

Claim 10 has been amended to clarify the active agent being administered. Claims 11 and 12 have been amended to correct antecedent basis.

Rejection under 35 U.S.C. 102(b)

Claims 4, 5, 6, 10 and 11 were rejected under 35 U.S.C. 102(b) as disclosed by U.S. Patent No. 5,654,312 to Adrulis, et al. (claims 4-6) or WO 95/18606 by Aggrawal (claims . These rejections are respectfully traversed if applied to the amended claims.

It should be noted that these references are not of record in this case; only in the parent.

Amendments to the Claims

Claim 4 has been amended to delete reference to both rosacea and eczema, however, it is believed that the amendment to claim 4 to refer to a method of treating symptoms associated with angiogenesis distinguishes over any of the cited art. Claim 4 has been amended to that it is clear that the treatment is to prevent angiogenesis, and thereby prevent the symptoms associated with angiogenesis, by administering an effective amount of an angiogenesis inhibitor. The dosages, as well as the formulation, and site of administration, will be different for treatment of the symptoms associated with angiogenesis as compared to other symptoms, such as those caused by inflammation. Support for this amendment is found in the application at page 14, lines 28-29 and page 11, lines 1-4.

Claim 10 has been amended to refer to a method of treating symptoms associated with elevated basic fibroblast growth factor, as discussed at page 15, lines 7-25. Claim 10 was also amended to delete basal cell sarcoma, squamous cell carcinoma and psoriasis.

Andrulis

Andrulis teaches that inflammatory and autoimmune dermatoses and acne (col. 6, line 33, to col. 7, line 31) can be treated with thalidomide. Rosacea is listed at col. 6, line 57. Eczema of the types caused by immune interactions is listed at col. 6, lines 39-43.

Claim 4 (and claims dependent thereon) is drawn to a method for inhibiting the symptoms associated with angiogenesis in lymphangiogenesis, Sturge-Weber syndrome, verruca vulgaris, neurofibromatosis, tuberous sclerosis, recessive dystrophic epidermolysis bullosa, venous ulcers, molluscum contagious, seborrheic keratosis, and actinic keratosis comprising

Claims 4 and 5 were rejected under 35 U.S.C. §103 as obvious over Japanese Patent 10120558. Claim 12 was rejected under 35 U.S.C. 103 as obvious over Aggarwal, et al. and "applicant's admission" and Dirpiro, et al. Pharmacotherapy. A Pathophysiologic Approach. 960-961 (1989). These rejections are respectfully traversed if applied to the amended claims.

JP10120558a

As discussed above, claims 4, 5, 7 and 8 are drawn a method of treating lymphangiogenesis, Sturge-Weber syndrome, verruca vulgaris, neurofibromatosis, tuberous sclerosis, recessive dystrophic epidermolysis bullosa, venous ulcers, molluscum contagious, seborrheic keratosis, and actinic keratosis by application of an effective amount of an angiogenesis inhibitor. Eczema has been deleted from the claim.

The JP discloses a topically applied composition including capsaicin, sinapine, and curcumin. This is nothing teaching the use of curcumin as the active ingredient, much less what an effective amount of curcumin would be, IF it were known that it was the active ingredient. Both capsaicin and sinapine are known to be pharmaceutically active. There is no disclosure of a pharmaceutical carrier for application to the skin, and in fact the teaching which extends not only to the skin but also hair growth, digestive juice secretion, sweating, laxation and urination, leads one to believe that the agent must be administered systemically (albeit transdermally) in order to have the intended effect. There is no teaching as to what constitutes an effective dosage. Since the claim no longer encompasses eczema, there can be no teaching in the JP that would make obvious the claimed subject matter. As demonstrated by the enclosed printout, the cause of eczema is not known and there are no known treatments. Therefore one skilled in the art would

not be led by the use of a formulation in which the curcumin is not the active ingredient to use curcumin or another anti-angiogenic factor as the active compound to treat eczema.

Aggarwal

As discussed above, claim 12 no longer encompasses treatment of psoriasis, basal cell carcinoma, and squamous cell carcinoma. Aggarwal teaches that curcumin is used to prevent proliferation of cells or inhibit phosporylase kinase; not that it inhibits bFGF or angiogenesis, and what an effective dosage would be for this purpose. Accordingly, one would not be motivated by the disclosure of Aggarwal to treat a patient for symptoms of diseases associated with elevated levels of bFGF.

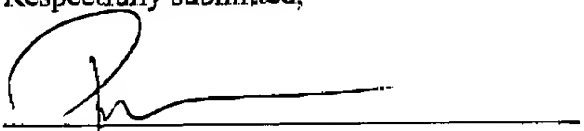
Pharmacotherapy

The Pharmacotherapy describes administration of tetracyclines or minocyclines topically to treat acne. The amount of the drug is the amount effective to kill bacterial flora. This is not the same amount as is required for the composition to be effective as an anti-angiogenic formulation. The examiner agrees with this but then says it is obvious to optimize the amount so that it would become effective as an anti-angiogenic formulation. It is clear that the mechanisms of action, and therefore the effective dosages, are different. The effective dosage of the tetracycline is considerably greater for inhibition of angiogenesis than for antibacterial activity. Although it is believed this rejection is totally improper, acne has been deleted from the claim solely to facilitate prosecution.

Allowance of Claims 4, 5, 7, 8, 9 and 13-17, as amended, and claim 18, is earnestly solicited.

U.S.S.N.: 09/345,712
Filed: June 30, 1999
AMENDMENT AND RESPONSE TO OFFICE ACTION

Respectfully submitted,



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Appendix: Marked Up Copy of Amended Claims

4. (twice amended) A method for inhibiting symptoms associated with angiogenesis in the treatment of skin disorders selected from the group consisting of lymphangiogenesis, Sturge-Weber syndrome, verruca vulgaris, neurofibromatosis, tuberous sclerosis, recessive dystrophic epidermolysis bullosa, venous ulcers, [rosacea, eczema,] molluscum contagious, seborrheic keratosis, and actinic keratosis comprising administering to the individual in need of treatment thereof an angiogenesis inhibitor in an amount effective to inhibit angiogenesis.

5. The method of claim 4 wherein the angiogenesis inhibitor is applied topically.

6. The method of claim 5 wherein the angiogenesis inhibitor is selected from the group consisting of collagenase inhibitors, endostatin, angiostatin, fumagillin derivatives like TNP-470, 2,5-diaryltetrahydrofurans, aminophenylphosphonic acid compounds, 3-substituted oxindole derivatives, thalidomides, penicillamine and IL12.

10. (twice amended) A method to treat the symptoms associated with elevated basic fibroblast growth factor in a disorder selected from the group consisting of angiosarcoma, hemangioendothelioma, [basal cell carcinoma, squamous cell carcinoma,] malignant melanoma and Karposi's sarcoma[, and psoriasis], comprising administering to the individual in need of treatment an effective amount of a curcuminoid to inhibit angiogenesis [of a curcuminoid].

11. (amended) The method of claim 10 wherein the [angiogenesis inhibitor] curcuminoid is curcumin.

12. (amended) The method of claim 10 wherein the [angiogenesis inhibitor] curcuminoid is demethoxycurcumin.

Please cancel claims 13-16.

17. (amended) A method for inhibiting skin disorders selected from the group consisting of lymphangiogenesis, hemangioma of childhood, Sturge-Weber syndrome, verruca vulgaris, neurofibromatosis, tuberous sclerosis, pyogenic granulomas, recessive dystrophic epidermolysis bullosa, venous ulcers, [acne,] rosacea, eczema, molluscum contagious, seborrheic keratosis, and actinic keratosis comprising administering to the individual in need of treatment thereof an angiogenesis inhibitor in an amount effective to inhibit angiogenesis, wherein the angiogenesis inhibitor is selected from the group consisting of

tetracyclines inhibiting collagenase,

endostatin,

a sulfated polysaccharide which inhibits angiogenesis.

Please add new claim 18.

18. The method of claim 10 wherein the disorder is malignant melanoma.

APPENDIX: Clean Copy of Claims as Amended

1 ~~4.~~ (twice amended) A method for inhibiting symptoms associated with angiogenesis in the treatment of skin disorders selected from the group consisting of lymphangiogenesis, Sturge-Weber syndrome, verruca vulgaris, neurofibromatosis, tuberous sclerosis, recessive dystrophic epidermolysis bullosa, venous ulcers, molluscum contagious, seborrheic keratosis, and actinic keratosis comprising administering to the individual in need of treatment thereof an angiogenesis inhibitor in an amount effective to inhibit angiogenesis.

2 ~~5.~~ The method of claim 4 wherein the angiogenesis inhibitor is applied topically.

3 ~~6.~~ The method of claim 5 wherein the angiogenesis inhibitor is selected from the group consisting of collagenase inhibitors, endostatin, angiostatin, fumagillin derivatives like TNP-470, 2,5-diaryltetrahydrofurans, aminophenylphosphonic acid compounds, 3-substituted oxindole derivatives, thalidomides, penicillamine and IL12.

4 ~~10.~~ (twice amended) A method to treat the symptoms associated with elevated basic fibroblast growth factor in a disorder selected from the group consisting of angiosarcoma, hemangioendothelioma, malignant melanoma and Karposi's sarcoma, comprising administering to the individual in need of treatment an effective amount of a curcuminoid to inhibit angiogenesis.

5 ~~11.~~ (amended) The method of claim 10 wherein the curcuminoid is curcumin.

6 ~~12.~~ (amended) The method of claim 10 wherein the curcuminoid is demethoxycurcumin.

Please cancel claims 13-16.

SUB C3 7 17. (amended) A method for inhibiting skin disorders selected from the group consisting of lymphangiogenesis, hemangioma of childhood, Sturge-Weber syndrome, verruca vulgaris, neurofibromatosis, tuberous sclerosis, pyogenic granulomas, recessive dystrophic epidermolysis bullosa, venous ulcers, rosacea, eczema, molluscum contagious, seborrheic keratosis, and actinic keratosis comprising administering to the individual in need of treatment thereof an angiogenesis inhibitor in an amount effective to inhibit angiogenesis, wherein the angiogenesis inhibitor is selected from the group consisting of

tetracyclines inhibiting collagenase,

endostatin,

a sulfated polysaccharide which inhibits angiogenesis.

R35 8 ~~18.~~ The method of claim 10 wherein the disorder is malignant melanoma.

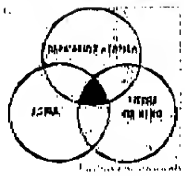
All About Atopic Dermatitis

What is Atopic Dermatitis?

Atopic Dermatitis (AD) is a disease that causes itchy, inflamed skin. It typically affects the insides of the elbows, backs of the knees, and the face, but can cover most of the body. AD falls into a category of diseases called atopic, a term originally used to describe the allergic conditions asthma and hay fever. AD was included in the atopic category because it often affects people who either suffer from asthma and/or hay fever or have family members who do. Physicians often refer to these three conditions as the "atopic triad."

AD is not contagious. Research indicates that atopic diseases like AD are genetically determined, inherited from one's parents. A child with one parent who has an atopic condition has a one-in-four chance of having some form of atopic disease. If both parents are atopic, the child has a greater than one-in-two chance of being atopic.

AD almost always begins in childhood, usually during infancy. Its symptoms are dry, itchy, scaly skin, cracks behind the ears, and rashes on the cheeks, arms, and legs. It alternately improves and worsens. During "flare-ups," open weeping or crusted sores may develop from the scratching or from infections.



Often the problem fades during childhood, though people with AD have a lifelong tendency to have:

- Dry skin—easily irritated
- Occupational skin disease—hand dermatitis
- Skin infections—Staph and herpes ("cold sores")
- Eye problems—eyelid dermatitis, cataracts
- Family and social relationships disrupted
- Work loss

Children affected by AD may suffer from asthma and hay fever at the same time, or one or both of these conditions may develop later. These diseases usually appear before age 30 and often continue throughout life.

AD is a very common disease, present worldwide, though it is more common in urban areas a developed countries. An estimated 10% of all people are at some time affected by AD (may not apply in the tropics.) It affected men and women of all races equally.

Is eczema the same as AD?

Eczema is a general term for any type of dermatitis of "inflammation of the skin." Atopic dermatitis (AD) is the most severe and chronic (long-lasting) kind of eczema. Although the

term eczema is often used for atopic dermatitis, there are several other skin diseases that are eczemas as well, including:

atopic dermatitis	seborrheic dermatitis
nummular eczema	irritant contact dermatitis
dishydrotic eczema	allergic contact dermatitis

All types of eczema cause itching and redness, and some will blister, weep, or peel.

What sets off AD?

AD tends to flare-up when the person is exposed to certain trigger factors—substances or conditions which worsen the dermatitis, such as dry skin, irritants, allergens, emotional stress, heat and sweating, and infections. The key to controlling AD is avoiding or reducing such exposure.

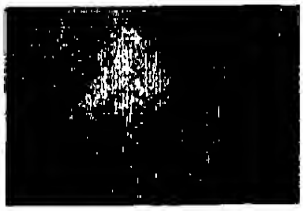
People with atopic diseases are usually sensitive to certain agitating substances. Some of these substances are irritants and some are allergens.

Irritants are substances that cause burning, itching, or redness, such as solvents, industrial chemicals, detergents, fumes, tobacco smoke, paints, bleach, woolen fabrics, acidic foods, astringents and other alcohol-containing skin care products, and some soaps and fragrances. If an irritant is potent, or concentrated enough, it can irritate anyone's skin, whether they have AD or not.

Allergens are more subtle trigger factors. An allergen does not irritate, but may trigger an AD flare-up in those who have become allergic to it from prior exposure. Allergens are usually animal or vegetable proteins from foods, pollens, or pets.

When people with AD are exposed to an irritant or allergen to which they are sensitive, inflammation-producing cells come into the skin. There, they release chemicals that cause itching and redness. Further damage occurs when the person scratches and rubs the affected area.

All AD sufferers must avoid irritants, while those with known allergies should likewise avoid allergens. Detecting an allergic substance can be difficult, as discussed below.



What about food allergies?

Food allergies can cause flare-ups. Since an allergic reaction to food (either by skin contact during food preparation or by eating the food) can trigger an AD flare-up, it is important to identify the trigger foods.

Diagnosing food allergies is extremely difficult. The surest way is to observe a worsening of eczema when a particular food is eaten. Sometimes this is only a coincidence with flaring

and needs to be verified with a food challenge, where the suspected food is eaten in the doctor's office. Withholding foods should be done only under the supervision of a physician as serious nutritional damage can be caused by the elimination of foods suspected to cause flare-ups. Patients are seldom allergic to more than one or two foods.

A skin test, made by scratching the skin with the suspected allergen, is helpful if the test is negative (indicating that the particular food will not affect the patient). If the scratched area becomes inflamed, the test is considered positive. Unfortunately, positive results are difficult to interpret and are accurate only about 20% of the time. At best, positive tests provide a clue to a possible allergy but should not be accepted as the last word. Additionally, because the skin of AD sufferers is so sensitive, simply scratching it can cause inflammation, making the likelihood of a false-positive skin test even higher.

A blood test is another type of test to detect food allergies. Blood tests, also, have a very high rate of false positive and they are expensive. For these reasons, they are not recommended for allergy testing in people with AD.

What about other allergies?

Occasionally people with AD notice a worsening of their condition when exposed to airborne allergens, such as pets or dusty rooms. An allergy to dust mites (tiny organisms present in household dust) may worsen AD in some people.

As with foods, positive scratch and blood tests are not very reliable for diagnosing an allergy to airborne substances. Research is being done on a "patch test" in which the suspected allergen is placed on the surface of the skin under a protective bandage. For now, however, the best approach is still the trial-and-error challenge method, under physician observation.

Allergy shots do not seem helpful for people with AD. In some cases, AD actually worsens during allergy shot therapy, even as the allergy symptoms are improving.

What about emotional stress?

Many older AD children and adults recognize a relationship between stressful occurrences in their lives and their AD flare-ups. Anger, frustration, and embarrassment all may cause flushing and itching. The resultant scratching can cascade into perpetuating dermatitis.

People with AD can learn how to avoid stress-triggered flare-ups. Two key concepts are involved:

1. coping with psychologically stressful events
2. controlling scratching behavior

What about climate, heat, humidity?

Extreme cold or hot temperatures, or sudden changes in the temperature, are poorly tolerated by persons with AD. High humidity causes increased sweating and may result in prickly-heat-type symptoms. Low humidity dries the skin, especially during winter months when homes are heated. Unfortunately, humidifiers do not help much; the best protection against "winter itch" is regular application of a good moisturizer. While you can do little about the climate (and moving to a new climate is often not possible, anyway), you can try to keep your home environment comfortable. Keeping thermostats set low and wearing fewer bedclothes, to prevent night sweating, are two ways to combat the problem.

What about exercise?
The only problem with exercise is that the resultant sweating generally causes itching. Layers of clothing can be removed to avoid overheating. Strenuous exercise is best avoided when a flare-up occurs.

What can be done when AD flares-up?
The best line of defense against AD is prevention, but flare-ups rarely can be avoided. Once inflammation begins, prompt treatment as directed by a physician is needed. Bathing or wet compresses may ease the itch.

Cortisone (steroid) creams applied directly to the affected area are helpful and a mainstay of therapy. Overuse of highly potent steroids can be damaging. Cortisone pills or shots are sometimes used, but they are not safe for long-term use. Researchers are seeking new and safer drugs to control the itch and inflammation.

Another treatment option is the use of ultraviolet light or sunlamps. Under a physician's supervision, some AD sufferers find this treatment helps. Tar baths, antihistamines, and antibiotics are often used, but these, too, meet with limited success. Treatments that don't seem to work include vitamins, mineral supplements, enriched diets, or nutritional supplements.

What can be done about dry skin?
AD sufferers always have very dry, brittle skin. The external layer of the skin, called the stratum corneum, acts as a protective barrier. When the stratum corneum cracks because of dryness, irritants can reach the sensitive layers below and cause a flare-up of AD.

Using moisturizers is the best and safest treatment to prevent dry skin. Moisturizers trap water beneath the skin, making it flexible and less likely to crack.

Research has found that the most effective moisturizers are ointment bases such as petrolatum. Cream base products are also helpful. Moisturizers work best when applied to damp skin. Lotions contain water and alcohol which can actually dry the skin and are usually inadequate for the dry skin of atopics.

People with AD can bathe regularly and use mild skin cleansers as long as they follow these simple rules:

—use warm, not hot, water
—avoid excessive scrubbing and toweling
—apply a moisturizer to the skin within 3 minutes after bathing

What can be done about infections?
People with AD are prone to skin infections, especially staph and herpes. In general, infections are hard to prevent but should be treated promptly to avoid aggravating the AD. It is important that persons with AD, or their parents, learn to recognize the early signs of skin infections and consult a physician immediately. Signs to watch for include increased redness, pus-filled bumps (pustules), and cold sores or fever blisters.

Sometimes viral illnesses such as colds or flu cause AD flare-ups. Worsening can be avoided by taking extra skin care while the virus runs its course.

Can sufferers of AD live normal lives?

Yes! People with AD do not have to be limited by their disease. It can be controlled by prevention, medication, and careful adherence to a treatment program supervised by a doctor.

Suggestions for treatment and control:

- **Establish a skin care routine.** Following the physician's instructions is crucial for keeping AD under control. This takes a lot of time and effort. Some sufferers may resent the effort or even deny that their skin needs special care. Resentment and denial are natural reactions to any disease. Failure to overcome these reactions, however, can lead to additional behavior that is harmful to the skin, such as wearing fabrics that irritate the skin, missing skin treatments, and forgetting medications. Establish a schedule and a regular daily routine. Include skin care along with all other activities of daily living such as brushing and flossing teeth or washing dinner dishes. It is important to maintain a flexible attitude, so that when the dermatitis flares and extra skin care is needed, it can be worked into the routine.
- **Recognize stressful situations and events.** To cope with the stress in your life, you must first notice when and how often stressful situations arise. These include day-to-day hassles as well as major events such as a job change, money problems, legal difficulties, family illness, etc. Ask yourself, "How do I react to stress? How does my body feel when I am stressed?"
- **Learn stress management techniques.** Certain approaches to reducing stress can be done on your own, such as setting priorities and organizing your time. Some activities that may reduce stress are regular aerobic exercise, hobbies, and meditation. Other approaches may require expert assistance such as a brief consultation with a psychologist.
- **Be aware of scratching.** Keep a record in a diary or calendar of times and situations when scratching is worst, and then try to limit your exposure to such situations. Many people with AD scratch the most during idle times. Engaging in a structured activity with other people or keeping busy with activities that involve the use of your hands may help prevent scratching
- **Control your environment.** Avoid irritants and allergens. Avoid low humidity. Wear cotton clothing. Guard against infection. Moisturize.

This information sets forth current opinions from recognized authorities, but it does not dictate an exclusive treatment course. Persons with questions about a medical condition should consult a physician who is knowledgeable about that condition.

The National Eczema Association for Science and Education is a national, patient-oriented organization which is governed by a Board of directors and guided by a Scientific Advisory Committee comprised of physicians and scientists who donate their time and expertise. NEASE is entirely supported through individual and corporate contributions and is a 501(c)(3) tax-exempt organization. For additional information or to receive a sample of our quarterly newsletter, The Advocate, please contact:

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